Clinical outcome of conservative therapy with transurethral resection for patients with invasive bladder cancer who cannot tolerate cystectomy

AUTHOR(S):

Akamatsu, Shusuke; Kanamaru, Sojun; Takenawa, Jun; Soeda, Asaki

CLINICAL OUTCOME OF CONSERVATIVE THERAPY WITH TRANSURETHRAL RESECTION FOR PATIENTS WITH INVASIVE BLADDER CANCER WHO CANNOT TOLERATE CYSTECTOMY

Shusuke Akamatsu, Sojun Kanamaru, Jun Takenawa and Asaki Soeda

The Department of Urology, Nishi-Kobe Medical Center

Among patients with invasive bladder cancer, there are patients who cannot tolerate cystectomy due to high age or comorbidities. We retrospectively reviewed 27 patients who were treated conservatively with transurethral resection (TUR). All patients had undergone TUR and 5 patients had received subsequent pelvic radiation therapy. The survival and control of local symptoms were analyzed statistically. Sixteen patients died of bladder cancer and 4 died of other causes with a median survival of 10 months. Seven patients were alive at a median follow up of 36 months. Tumor stage, grade and hydronephrosis at diagnosis were related with survival. Hematuria, bladder tamponade, and lower urinary tract obstruction could be controlled with TUR. However, those patients who complained of bladder irritative symptoms at diagnosis were likely to develop uncontrollable bladder irritability. Conservative treatment with TUR alone was an acceptable option in terms of survival for stage II patients with a short life expectancy. Even at more advanced stages, most of the local symptoms could be controlled with TUR. However, in patients with bladder irritability at diagnosis, the merit of cystectomy may outweigh its risk even among high age patients or those with severe comorbidities.

(Hinyokika Kiyo **53** : 863–868, 2007)

Key words : Bladder carcinoma, Transurethral resection, Cystectomy, Conservative surgery

INTRODUCTION

Invasive bladder cancer is a life threatening disease that necessitates aggressive treatment. Radical cystectomy is the golden standard of treatment[1]. Even in the most advanced cases, cystectomy is occasionally performed to achieve local control of the disease if severe local symptoms develop. The safety of radical cystectomy in otherwise healthy elderly patients has been reported recently[2,3]. However, it is true that cystectomy tends to be avoided in elderly patients at high risk[4,5]. The quality of life (QOL) after urinary diversion also needs consideration, especially in elderly patients who require social support. It is still not clear who would benefit from cystectomy in this population. Transurethral resection (TUR) is not a curative treatment in invasive bladder cancer except in limited cases of radical TUR[6,7]. However, it can be effective in the control of symptoms and can improve the QOL of the patients who are not candidates for cystectomy. To date, there have been no reports on the survival and local control of the disease among high-risk patients who were conservatively treated with TUR. In this study, we aimed to assess if TUR could provide enough palliation of symptoms and maintain QOL, and identify those patients who would benefit from cystectomy even at high risk.

PATIENTS AND METHODS

PATIENTS

The records of 27 patients diagnosed with pathologically confirmed muscle invasive bladder cancer (≧pT2) who did not wish cystectomy and received conservative treatment with TUR between October 1999 and April 2005 at our institution were reviewed. Five patients had received subsequent pelvic radiation therapy (RT) of 50Gy. The patients who received chemotherapy were excluded from this study. All the patients were either alive at the time of analysis or had been followed at our institution until death. The patients were preoperatively evaluated from various aspects, including age, performance status and comorbidities. Nineteen patients chose conservative treatment due to high age (mean age, 84.3±3.7, range 79–91) and 4 patients chose conservative treatment due to the presence of high-risk comorbidities. Four patients who refused cystectomy in the absence of a high age or comorbidities were also included in the analysis. Of the four patients who avoided cystectomy due to comorbidities, two were in Eastern Cooperative Oncology Group (ECOG) performance status 4, one had severe ischemic heart disease and cerebrovascular disease, and one had received surgery and radiation therapy due to advanced uterine carcinoma.

STAGING

TNM classification was determined using either computerized tomography (CT) or magnetic resonance images (MRI) of the abdomen and pelvis, chest CT, and bone scans. Since T2a and T2b, or T3a and T3b could not be discriminated either by CT or MRI, they were categorized together into T2 and T3, respectively. American Joint Committee on Cancer (AJCC) stages were also recorded.

TUMOR LOCATION AND CONCOMITANT CARCINIMA IN SITU PRESENTATION

The locations of the main tumors were recorded as trigone, posterior wall, dome, anterior wall, left wall, and right wall. Data on the concomitant presence of carcinoma in situ (CIS) were lacking in most of the pathological reports and therefore could not be collected.

PRESENTING CONDITIONS

ECOG performance status and typical subjective and objective symptoms at diagnosis were recorded to identify factors that would predict the development of severe local symptoms. The symptoms and signs recorded were macroscopic hematuria, bladder tamponade, bladder irritative symptoms, and unilateral or bilateral hydronephrosis. Bladder irritative symptoms included frequent urination, urgency, dysuria and local pain. Local pain was included in irritative symptoms since pain in bladder cancer patients is often difficult to discriminate from other irritative symptoms. Table 1 shows the clinical characteristics of the 27 patients.

STATISTICAL ANALYSIS

Survival rates were calculated according to the Kaplan-Meier method and the differences in survival between subgroups were tested with a log rank test. Fisher's exact test was used to examine the association between clinical variables. A p value less than 0.05 was indicative of a statistically significant difference.

RESULTS

SURVIVAL

Of the 27 patients reviewed, 16 (59.3%) died of disease and 4 (14.8%) died of other causes with a median survival of 10 months. Six patients (22.2%) were alive with disease, and 1 (3.7%) was alive without disease with a median follow up of 36 months. None of those patients who were alive with disease had distant metastasis at the time of analysis. Univariate analysis was performed to determine the clinical variables that were predictive of disease-specific survival (Table 2). T stage, M stage, tumor grade and AJCC stages were related with survival. AJCC Stage II patients had significantly higher disease-specific survival rates ($p=0.008$) than stage III-IV patients. The survival rate at 2 years for Stage II patients was 68.6% (Fig. 1). Grade 2 tumors had higher disease-specific survival rates ($p=0.036$) compared with grade 3 tumors. Presence of hydronephrosis at diagnosis was also related with survival ($p=0.003$, Fig. 2). Radiation therapy did not improve disease-specific survival. Performance status and other symptoms and signs were not related with either overall or disease-specific survival.

Table 1. Patient characteristics

Mean age ±SD	79.9±8.7
No. gender	
Male	20
Female	7
No. cell type	
Transitional cell carcinoma	23
Adenocarcinoma	1
Small cell carcinoma	1
Undifferentiated	2
No. T stage at diagnosis	
T2	14
T3	9
T4	4
No. N stage at diagnosis	
N0	16
N1/N2	8
Unknown	3
No. M stage at dianosis	
M0	19
M1	5
Unknown	3
No. tumor grade by TUR	
G2	6
G3	19
Unknown	2
No. stage grouping	
Stage II	8
Stage III	3
Stage IV	13
Unknown	3
Tumor location	
Trigone	7
Posterior wall	8
Dome	1
Anterior wall	2
Right wall	4
Left wall	5
No. performance status at diagnosis	
0	3
1	16
2	1
3	4
4	3
Symptoms and signs present at diagnosis (%)	
Hematuria †	18 (67%)
Bladder tamponade	3 (11%)
Bladder irritative symptom	9 (33%)
Hydronephrosis	9 (33%)

† Patients with bladder tamponade are included.

LOCAL SYMPTOMS

Upper urinary tract obstruction necessitating urinary

Table 2. Univariate analysis of potential prognostic factors with respect to disease specific survival (log-rank test)

Prognostic factor	Categories	p value
Age	<80/≥80	0.197
Performance Status	0-2/3-4	0.592
Cell Type	TCC/non-TCC	0.200
T stage	T2/T3 and T4	0.015
N stage	N0/N1 and N2	0.116
M stage	M0/M1	<0.001
Grade	Grade 2/Grade 3	0.036
Stage grouping	Stage II/Stage III and IV	0.009
Bladder irritative symptom at diagnosis	Yes/No	0.309
Hydronephrosis at diagnosis	Yes/No	0.003
Radiation therapy	Yes/No	0.287

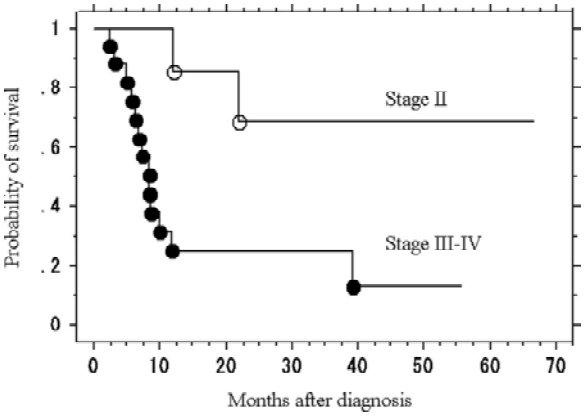

Fig. 1. Disease-specific survival of stage II (n=8), and stage III-IV (n=18) patients.

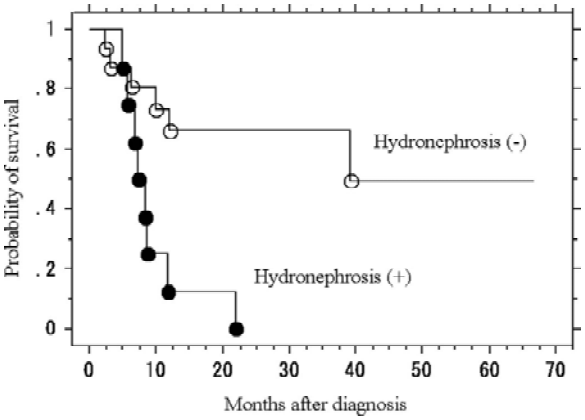

Fig. 2. Disease-specific survival of 25 patients stratified by the presence (n=9) or absence (n=16) of hydronephrosis at diagnosis.

diversion, bladder tamponade, lower urinary tract obstruction, and severe bladder irritative symptoms were analyzed to evaluate the control of local symptoms. Urinary diversion was ultimately necessary in 7 patients due to upper urinary tract obstruction. The method of urinary diversion was ureterocutaneostomy in 4 patients, percutaneous nephrostomy in 2 patients, and ureteral stent in 1 patient. The necessity of urinary diversion was not statistically related to tumor stage or the presence of hydronephrosis at diagnosis. Bladder tamponade was seen in 8 patients, and 4 of them had recurrent episodes. However, in all the cases, hematuria could be controlled with TUR. Of the 4 patients with recurrent episodes, 3 patients had received TUR with clot evacuation twice, and 1 patient had received transurethral fulguration five times mainly due

Table 3. Characteristics of those who developed severe bladder iriitability

Variable	With bladder irritability (n=6)	Without bladder irritability (n=21)	p value
T stage			
T2	2	12	0.385
T3, T4	4	9	
N stage			
N0	2	14	0.129
N1, N2	4	4	
Unknown (n=3)			
M stage			
M0	3	16	0.079
M1	3	2	
Unknown (n=3)			
Grade			
Grade 2	0	6	0.289
Grade 3	5	14	
Unknown (n=2)			
Stage grouping			
Stage II	1	5	0.628
Stage III, stage IV	5	13	
Unknown (n=3)			
Presenting symptoms and signs			
Hematuria			
Yes	5	13	0.628
No	1	8	
Bladder tamponade			
Yes	2	1	0.115
No	4	20	
Bladder irritative symptom			
Yes	5	3	0.004
No	1	18	
Hydronephrosis			
Yes	3	6	0.630
No	3	13	
Unknown (n=2)			
Radiation therapy			
Yes	1	4	>0.999
No	4	17	
Excluded (n=1)†			

† 1 had received previous radiation therapy due to uterine carcinoma.

to cystitis after radiation therapy for uterine carcinoma. Transfusion was necessary because of hematuria in 3 patients. No risk factor for developing bladder tamponade could be identified. Lower urinary tract obstruction was observed in 4 patients; however, with TUR, all could be freed from indwelling catheters. Six patients suffered from severe bladder irritative symptoms. TUR alone could not alleviate severe bladder irritability, and in 5 patients, symptoms did not disappear completely even with a high enough dose of opioid. To identify the variables related with developing severe bladder irritability, univariate analysis was performed (Table 3). The presence of bladder irritative symptoms at diagnosis was the only variable that showed statistical significance ($p=0.004$). The presence of trigone involvement was not related to the presence of bladder irritative symptoms at diagnosis or subsequent development of severe bladder irritability. Radiation therapy was not related to hydronephrosis, bladder tamponade, lower urinary tract obstruction or severe bladder irritative symptoms.

DISCUSSION

Tumor stage and grade are known to be the strongest predictors of cancer-specific survival[8]. Hydronephrosis is also reported to be one of the predictors of survival[9,10]. Our data confirmed that tumor stage, grade, and hydronephrosis were predictors of disease-specific survival in patients treated with TUR alone. Our data also showed that in patients with stage II disease, a 2-year disease-specific survival of 68.6% can be obtained with TUR alone. Other investigators have also shown that TUR can control some muscle invasive bladder cancer that does not penetrate the bladder muscle[11,12]. Hollenbeck et al. showed with a Kaplan-Meier curve that 2 year disease-specific survival after cystectomy and TUR-BT for stage II diseases among the patients over 80 years old was between 70–80% and 50–60%, respectively[3]. They also reported that the overall survival in this patient group at 2 years after cystectomy was less than 50%. This shows that although cystectomy improves survival the most in this age group, about half of the patients die before 2 years after surgery either from bladder cancer or from other causes even if they could tolerate cystectomy.

Trimodality treatment combining TUR, chemotherapy and radiotherapy is emerging as an alternative to cystectomy in treating muscle invasive tumor. By adding chemotherapy and radiotherapy, small early stage tumors, which were visibly and microscopically completely resected by TUR show excellent overall survival almost equivalent to that after cystectomy[13]. However, chemotherapy poses certain risks and radiotherapy can worsen local symptoms if severe radiation cystitis develops. It is still not clear if the patients who have more advanced diseases or who are not expected to live long due to severe comorbidities really benefit from addition of chemotherapy and radiotherapy.

Although multiple TUR and transfusions were necessary in some patients, most of the local symptoms could be adequately controlled with TUR alone, except for bladder irritative symptoms. Bladder irritative symptoms are often difficult to manage and significantly lower QOL. Takashi et al.[14] and Thrasher et al.[15] reported that irritative symptoms were one of the predictors of prognosis by multivariate analysis. In the present study, although irritative symptoms were not related to survival, the presence of irritative symptoms at diagnosis was predictive of developing more severe irritative symptoms that could not be controlled even with a high enough dose of opioid. Therefore, even those patients at high risk, who present with bladder irritative symptoms might benefit from cystectomy to maintain QOL. The factors that account for these bladder irritative symptoms are still not clear. Although the presence of tumors in the trigone may be the culprit of bladder irritative symptoms, our study failed to show any association. The presence of associated CIS, which we could not analyze in our study, may explain these symptoms and requires further investigation.

Safety of cystectomy in elderly patients has been previously reported. Chang et al. reported that radical cystectomy is safe even in elderly patients at high risk[16]. However, perioperative safety alone is not sufficient in deciding treatment options, especially in high-risk patients who are not candidates for a neobladder and require a stoma. The presence of a stoma lowers QOL compared with having an intact bladder[17,18]. Our study suggests that treatment with TUR alone can be a treatment option in stage II patients with a short life expectancy due to other causes both in terms of survival and local disease control. Conservative therapy with TUR alone is also an effective method of local disease control for the patients with T4 disease or those with distant metastasis who cannot tolerate chemotherapy, since there is little merit of cystectomy in these cases[19]. However, when severe irritative symptoms are present at diagnosis in the absence of T4 disease or distant metastasis, the merit of cystectomy may outweigh the risk of cystectomy even in elderly patients or those with comorbidities, since severe uncontrollable bladder irritability is likely to develop in the future.

CONCLUSION

We found that tumor stage, grade, and presence of hydronephrosis were related with survival. Treatment with TUR alone can be an option for stage II patients with a short life expectancy. Even at more advanced stages, most of the symptoms could be adequately controlled with TUR; however, cystectomy should be considered when bladder irritative symptoms are present at diagnosis.

REFERENCES

1) Stein JP, Lieskovsky G, Cote R, et al. : Radical cystectomy in the treatment of invasive bladder cancer : long-term results in 1,054 patietns. J Clin Oncol **19** : 666–675, 2001
2) Soulie M, Straub M, Game X, et al. : A multicenter study of the morbidity of radical cystectomy in select elderly patients with bladder cancer. J Urol **167** : 1325–1328, 2002
3) Hollenbeck BK, Miller D, Taub D, et al. : Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older. Urology **64** : 292–297, 2004
4) Konety BR and Joslyn SA : Factors influencing aggressive therapy for bladder cancer : an analysis of data from the SEER program. J Urol **170** : 1765–1771, 2003
5) Prout GR, Wesley MN, Yancik R, et al. : Age and comorbidity impact therapy in older bladder carcinoma patients. Cancer **104** : 1638–1647, 2005
6) Solsona E, Iborra I, Ricos JV, et al. : Feasibility of transurethral resection for muscle- infiltrating carcinoma of the bladder : prospective study. J Urol **147** : 1513–1517, 1992
7) Herr HW : Transurethral resection of muscle-invasive bladder cancer ; 10 year outcome. J Clin Oncol **19** : 89–93, 2001
8) Narayana AS, Loening SA, Slymen DJ, et al. : Bladder cancer : factors affecting survival. J Urol **130** : 56–60, 1983
9) Haleblian GE, Skinner EC, Dickinson MG, et al. : Hydronephrosis as a prognostic indicator in bladder cancer patients. J Urol **160** : 2011–2014, 1998
10) Michaelson MD, Shipley WU, Heney NM, et al. : Selective bladder preservation for muscle- invasive transitional cell carcinoma of the urinary bladder. Br J Cancer **90** : 578–581, 2004
11) Barnes RW, Dick AL, Hadley HL, et al. : Survival following transurethral resection of bladder carcinoma. Cancer Res **37** : 1895–1899, 1977
12) Henry K, Miller J and Mori M : Comparison of transurethral resection to radical therapies for stage B bladder tumors. J Urol **140** : 964–965, 1998
13) Rödel C, Weiss C and Sauer R : Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol **24** : 5536–5543, 2006
14) Takashi M, Murase T, Mizuno S, et al. : Multivariate evaluation of prognostic determinants in bladder cancer patients. Urol Int **42** : 368–374, 1987
15) Thrasher JB, Frazier HA, Robertson JE, et al. : Clinical variables which serve as predictors of cancer-specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. Cancer **73** : 1708–1715, 1994
16) Chang SS, Alberts G, Cookson S, et al. : Radical cystectomy is safe in elderly patients at high risk. J Urol **166** : 938–941, 2001
17) Jones MA, Breckman B and Hendry WF : Life with an ileal conduit : results of questionnaire surveys of patients and urological surgeons. Br J Urol **52** : 21–25, 1980
18) Studer U and Furger P : Die psycho-soziale reintegration des urostomapatienten. Schweiz Med Wochenschr **111** : 1834–1839, 1981
19) Gschwend JE, Fair WR and Vieweg J : Radical cystectomy for invasive bladder cancer : contemporary results and remaining controversies. Eur Urol **38** : 121–130, 2000

(Received on January 11, 2007
Accepted on June 8, 2007)

和文抄録

膀胱全摘術に耐えられないハイリスク患者における浸潤性膀胱癌に対する経尿道的切除術による保存的加療の検討

赤松　秀輔，金丸　聰淳，武縄　　淳，添田　朝樹
西神戸医療センター泌尿器科

［背景と目的］浸潤性膀胱癌の患者の中には高齢や併存疾患などのリスクにより膀胱全摘術に耐えられない者がいる．われわれは，これらの患者の中で経尿道的手術により保存的に加療した者についてレトロスペクティブに検討した．

［方法］27例につき検討した．全例で経尿道的手術を行い，5例で骨盤内への放射線治療を追加した．生存，および局所症状のコントロールについて統計学的に解析をした．

［結果］16例が癌死，4例が他因死した．生存期間の中央値は10カ月であった．7例が生存していた．生存者の観察期間の中央値は36カ月であった．生存期間は腫瘍のステージ，グレード，および診断時の水腎症の有無と関係していた．血尿，膀胱タンポナーデ，および下部尿路閉塞は経尿道的手術によりコントロールが可能であった．しかし，初診時に膀胱刺激症状を有する患者は後にコントロールしがたい強い膀胱刺激症状を呈する傾向にあった．

［結語］ステージⅡの患者で余命の短い者に対しては経尿道的手術のみの治療は生存率の観点からも容認できる選択肢であった．より進行したステージであっても大半の局所症状は経尿道的手術でコントロール可能であった．しかし初診時に膀胱刺激症状を有する場合は例え高齢患者や重篤な合併症のある患者であっても膀胱全摘術の利点がリスクを上回る可能性がある．

（泌尿紀要 **53**：863-868，2007）